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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO |
|-----------------|-----------------|----------------------|-------------------------|-----------------|
| 10/653,350 | 09/02/2003 | Eun Jung Lee | A35967 073226.0119 | 3503 |
| 38485 | 7590 11/15/2006 | | EXAM | INER |
| ARENT FO | | | SEHARASEYON, | JEGATHEESAN |
| NEW YORK | | | ART UNIT | PAPER NUMBER |
| | | | 1647 | |
| | | | DATE MAILED: 11/15/2006 | 5 |

Please find below and/or attached an Office communication concerning this application or proceeding.

| | Application No. | Applicant(s) |
|--|--|---|
| | 10/653,350 | LEE ET AL. |
| Office Action Summary | Examiner | Art Unit |
| | Jegatheesan Seharaseyon, Ph.D | 1647 |
| The MAILING DATE of this communication app | | orrespondence address |
| Period for Reply | | |
| A SHORTENED STATUTORY PERIOD FOR REPLY WHICHEVER IS LONGER, FROM THE MAILING DA - Extensions of time may be available under the provisions of 37 CFR 1.13 after SIX (6) MONTHS from the mailing date of this communication. If NO period for reply is specified above, the maximum statutory period w - Failure to reply within the set or extended period for reply will, by statute, Any reply received by the Office later than three months after the mailing earned patent term adjustment. See 37 CFR 1.704(b). | ATE OF THIS COMMUNICATION 16(a). In no event, however, may a reply be tim rill apply and will expire SIX (6) MONTHS from a cause the application to become ABANDONEI | I. lely filed the mailing date of this communication. O (35 U.S.C. § 133). |
| Status | | |
| 1)⊠ Responsive to communication(s) filed on 30 Au | iaust 2006. | |
| • | action is non-final. | |
| 3) Since this application is in condition for allowan | | secution as to the merits is |
| closed in accordance with the practice under E | | |
| Disposition of Claims | | |
| 4)⊠ Claim(s) <u>1-10</u> is/are pending in the application. | | |
| 4a) Of the above claim(s) <u>3-5 and 10</u> is/are with | drawn from consideration. | |
| 5) Claim(s) is/are allowed. | | |
| 6)⊠ Claim(s) <u>1,2,6,7 and 9</u> is/are rejected. | | |
| 7)⊠ Claim(s) <u>8</u> is/are objected to. | | |
| 8) Claim(s) are subject to restriction and/or | election requirement. | |
| Application Papers | | |
| 9) The specification is objected to by the Examiner | r. | |
| 10)⊠ The drawing(s) filed on <u>02 September 2003</u> is/a | | ted to by the Examiner. |
| Applicant may not request that any objection to the | • | - |
| Replacement drawing sheet(s) including the correcti | ion is required if the drawing(s) is obj | ected to. See 37 CFR 1.121(d). |
| 11) ☐ The oath or declaration is objected to by the Ex | aminer. Note the attached Office | Action or form PTO-152. |
| Priority under 35 U.S.C. § 119 | | |
| 12)⊠ Acknowledgment is made of a claim for foreign | priority under 35 U.S.C. § 119(a) | -(d) or (f). |
| a)⊠ All b)□ Some * c)□ None of: | | |
| ☐ Certified copies of the priority documents | s have been received. | |
| 2. Certified copies of the priority documents | s have been received in Application | on No |
| Copies of the certified copies of the prior | ity documents have been receive | ed in this National Stage |
| application from the International Bureau | , , , , | |
| * See the attached detailed Office action for a list | of the certified copies not receive | d. |
| | | |
| Attachment(s) | | |
| 1) Notice of References Cited (PTO-892) 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) | 4) Interview Summary Paper No(s)/Mail Da | (PTO-413) ate. |
| 3) X Information Disclosure Statement(s) (PTO/SB/08) | 5) Notice of Informal P | |
| Paper No(s)/Mail Date <u>8/25/04</u> . | 5) L. Other | |

Application/Control Number: 10/653,350 Page 2

7

Art Unit: 1647

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-2 and 6-9, drawn to an isolated polypeptide in response filed 8/30/2006 is acknowledged. Applicant argues that a search of all of the claims would not be a burden, since the same search terms-e.g., "interferon" and "glycosylation' would be required for both the protein and its encoding DNA. Also, Applicant asserts that there is a well-known relationship between a polypeptide and its encoding DNA, rendering these molecules part of the same patentable invention. Applicants' arguments have been fully considered but are not considered to be persuasive because search for polypeptide will not automatically result identifying the polynucleotide. Similarly a search directed to polynucleotide will not automatically lead to the identification of the protein. Therefore, the searches for each of the groups are not coextensive and would be a burden on the Office to search all of the different claims of the groups. The requirement is still deemed proper and is therefore made FINAL. Claims 3-5 and 10 will be withdrawn from further consideration. Thus, claims 1-2 and 6-9 are pending and examined.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C.
 119(a-d) is acknowledged. Applicant is accorded the priority date of 8/31/2002.

Information Disclosure Statement

3. The IDS filed on 8/25/2004 has been considered.

Application/Control Number: 10/653,350 Page 3

Art Unit: 1647

Drawings

4. The drawings filed 9/2/2003 are acknowledged. Figure 8 is objected to because the western blot is not clear and provides no useful information.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5a. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human interferon alpha isoform of SEQ ID NO: 1, the specification does not reasonably provide enablement for all human interferon alpha isoforms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level

Application/Control Number: 10/653,350 Page 4

Art Unit: 1647

of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Claims 1-2 are drawn to human interferon alpha isoform comprising at least one N-glycosylation motif with sequence Asn-Xaa-Ser/Thr. However, Applicant's have only disclosed human interferon alpha of SEQ ID NO: 1 (pages 5, 7 and 8). The specification as filed is insufficient to enable one skilled in the art to practice the claimed invention without an undue amount of experimentation because not all human interferon alpha isoforms have been disclosed. The specification asserts that in human at least 20 kinds of interferon-alpha genes and pseudo-genes have been identified (see page 2). It also asserts that "isoform of human interferon alpha" refers to an analogue or mutant having one or more of amino acid sequence residues of wild-type human interferon alpha modified with another amino acid while maintaining its inherent activities. Applicant has not identified a common structure responsible for the "inherent activities". Since, not all human interferon alpha isoforms are disclosed and a common structure has not been identified, it is unclear how one skilled in the art can extrapolate the observations of the instant invention to obtain all human interferon alpha isoforms contemplated in the instant invention. The specification does not teach how to make amino acid sequences that is an analogue or mutant having one or more of amino acid sequence residues of wild-type human interferon alpha modified with another amino acid while maintaining its inherent activities.

Art Unit: 1647

Although, the biological functions of the interferon alpha polypeptides are well known it is not clear how the functions will be affected by changing one or more amino acid residues of the wild-type human interferon alpha. Since, one skilled in the art could not determine with reasonable expectation of success what biological functions of interferon alpha would remain in the analogue or mutant, the skilled artisan would not be able to make human interferon alpha mutants, and test them for biological activity. Furthermore, the specification provides no guidance as to how the skilled artisan could use human interferon alpha analogue or mutant, as no functional limitations associated with human interferon alpha analogue or mutant are recited in the claims.

Despite knowledge in the art for producing variants of a given polypeptide with amino acid deletions, insertions or substitutions the specification fails to provide any guidance regarding the changes/modifications contemplated and yet retain the function of the interferon alpha isoforms claimed. Furthermore, detailed information regarding the structural and functional requirements of the disclosed protein is lacking. Although it is accepted that the amino acid sequence of a polypeptide determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the

Art Unit: 1647

protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (Wells 1990, Ngo et al., 1994). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Therefore, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope, because the skilled artisan would have no reasonable expectation of being able to make and use interferon alpha isoform polypeptides with various identities for any purpose stated in the specification.

5b. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or

Art Unit: 1647

chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

The claims are drawn to interferon alpha isoform comprising at least one N-glycosylation motif with sequence Asn-Xaa-Ser/Thr. However, Applicant's have only disclosed human interferon alpha of SEQ ID NO: 1 (pages 5, 7 and 8). There is no functional characteristic associated with any specific motifs within the interferon alpha polypeptide has been identified. The specification as filed does not disclose all human interferon alpha isoforms. The specification asserts that in human at least 20 kinds of interferon-alpha genes and pseudo-genes have been identified (see page 2). It also asserts that "isoform of human interferon alpha" refers to an analogue or mutant having one or more of amino acid sequence residues of wild-type human interferon alpha modified with another amino acid while maintaining its inherent activities. The claims do not require that the claimed polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until

Art Unit: 1647

reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1616.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the human sequence.

In this case, the only factor present in the claim is a partial structural requirement in the form of a sequence motif needed for N-glycosylation (NXS/T). There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 1, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1647

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

- 1. Determining the scope and contents of the prior art.
- 2. Ascertaining the differences between the prior art and the claims at issue.
- 3. Resolving the level of ordinary skill in the pertinent art.
- 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6a. Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyman et al. (1998) in view of Margolin et al. (U. S. Patent No. 6, 359, 118).

Claims are drawn to human interferon alpha isoform comprising at least one N-glycosylation.

Nyman et al. discloses a recombinant interferon alpha isoform (IFN- α 14c) that contains at least a potential N-glycosylation (abstract, page 299). The glycosylation was

Art Unit: 1647

shown to occur at Asn-72 (abstract). This occurs in the non-helical region of the interferon alpha protein. The reference also teaches that Asn-72 is attached to a carbohydrate moiety with a molecular mass of approximately 1800 Daltons (page 301). Nyman et al. does not disclose asparagine-72 (Asn-72) being N-linked to acetylglucosamine.

Margolin et al. (U. S. Patent No. 6, 359, 118) teaches that the carbohydrate monomers typically attached to glycoproteins include galactose, mannose, glucose, N-acetylglucosamine, N-acetylgalactosamine, fucose, xylose, sialic acid and others (column 1, lines 45-48). The carbohydrate units are usually attached through the hydroxyl groups of serine and threonine side chains, or the amide nitrogen atom of asparagine side chains (column 1, lines 48-50). The reference also teaches that the addition of carbohydrate molecules make the protein stable while maintaining the structural and functional integrity of the glycoprotein backbone (column 1, line 10-20). The reference also teaches pharmaceutical compositions of the protein comprising the carbohydrate (column 14, lines 25-40).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the recombinant interferon alpha isoform comprising at least one N-glycosylated moiety as disclosed by Nyman et al. with the teachings of Margolin et al. to add N-acetylglucosamine motif at the asparagine residue. One of ordinary skill in the art would have been motivated to N-glycosylate recombinant interferon alpha isoform with N-acetylglucosamine because Nyman et al. teaches that recombinant interferon alpha isoform (IFN-α14c) is N-glycosylated at Asn-72 and

Art Unit: 1647

Margolin et al. teaches that carbohydrates are added thru the amide of asparagine side chains (column 1, lines 48-50) to increase the stability of the protein. Further, there is reasonable expectation of success because Nyman et al. discloses that there is N-glycosylation of recombinant interferon alpha isoform. In addition, Margolin et al. also disclose pharmaceutical composition. Therefore, the instant invention is *prima facie* obvious over Nyman et al. (1998) in view of Margolin et al. (U. S. Patent No. 6, 359, 118).

6b.Claims 6, 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goeddel et al. (U. S. Patent No. 6, 482, 613) in view of Sekellick et al. (U. S. Patent No. 6, 020, 465) and Apweiler et al. (1999).

The instant invention is drawn to IFN- α isoform with at least one introduced N-glycosylation.

Goeddel et al. (U. S. Patent No. 6, 482, 613) discloses recombinant human IFN-α isoform of SEQ ID NO: 1 in *E.coli* (see Appendix A). The reference also teaches that human leukocyte interferon is a glycosylated protein (column 3, lines 19-24). The reference also discloses the putative signal sequence that is 23 amino acids long (column 11, lines 50-53). Goeddel et al. reference discloses the expression of a "mature leukocyte interferon" connotes the bacterial or other microbial production of an interferon molecule unaccompanied by associated glycosylation (column 4, lines 23-26). The mature polypeptide starts at amino acid Cys. However, the reference does not specifically recite the N-glycosylation motif of NXS/T.

Art Unit: 1647

Apweiler et al. (1999) disclose the N-glycosylation consensus sequence NXS/T (where X can be any amino acid but proline) required for N-glycosylation of protein (abstract).

Sekellick et al. (U. S. Patent No. 6, 020, 465) discloses the use of mammalian cell culture (e.g. CHO cells) to produce recombinant proteins. The reference teaches that CHO cells are most preferred in order to achieve glycosylation (column 2, lines 5-10). The reference also teaches N-glycosylation protein increases stability (column 4, lines 17-25).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the recombinant interferon alpha isoform of SEQ ID NO: 1 disclosed by Goeddel et al. with the teachings of Apweiler et al. and Sekellick et al. to add a N-glycosylation motif and produce a glycosylated interferon. One of ordinary skill in the art would have been motivated to N-glycosylate recombinant interferon alpha isoform by modifying SEQ ID NO: 1 with NXS/T motif because Apweiler et al. teaches that NXS/T motif are required for N-glycosylation and provide for increased the stability of the protein as disclosed in Sekellick et al. In addition, Sekellick et al. teaches that producing polypeptides in mammalian cells such as CHO cells allows for the recombinant interferon alpha isoform to be N-glycosylated. Further, there is reasonable expectation of success because Goeddel et al. discloses that human leukocyte interferon is a glycosylated protein. In addition, modifying amino acids Pro4, Gln5, Thr6 or Thr6, His7, Ser8 or Leu26, Phe27, Ser28 or Ala50, Glu51, Thr52 or Lys134, Tyr135, Ser136 etc. for example, to introduce N-glycosylation motifs for

Art Unit: 1647

glycosylation of the interferon alpha isoform is obvious over the prior art because motivation is provided by the fact that these sequence motifs have Ser or Thr residue at the 3rd position as described by Apweiler et al. However, modifying His34, Asp35, Phe36 motif for example, to introduce the N-glycosylation appears to be unobvious because there is no motivation to select these amino acid positions for the modification in the absence of Ser or Thr residue at the 3rd position of the motif for N-glycosylation. Therefore, the instant invention is *prima facie* obvious Goeddel et al. (U. S. Patent No. 6, 482, 613) in view of Sekellick et al. (U. S. Patent No. 6, 020, 465) and Apweiler et al. (1999).

Conclusion

7. Claim 8 is objected and will be allowable if written independent of the rejected claim 7. Claims 1, 2, 6, 7 and 9 remain rejected.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon, Ph.D whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

Art Unit: 1647

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JS Art Unit 1647, November 8, 2006. Jagatheesen Schoraseyn.

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| | GenCore version 5.1.9 Copyright (c) 1993 - 2006 Biocceleration Ltd. |
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RESULT 1

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; Sequence 26, Application US/07145002B
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; Sequence 26, Application US/07145002B
; Patent No. 6482613
; Patent No. 6482613
; GENERAL INFORMATION:
; PAPLICANT: Goeddel, David V.
; APPLICANT: Gestka, Sidney
; TITLE OF INVENTION: MICROBIAL PRODUCTION OF MATURE HUMAN
; TITLE OF INVENTION: LEUKOCYTE INTERFERONS
; FILE REFERENCE: 1803-0088-999
; CURRENT APPLICATION NUMBER: US/07/145,002B
; CURRENT FILING DATE: 1989-01-19
; NUMBER OF SEQ ID NOS: 70
; SOFTWARE: FastSEQ for Windows Version 3.0
; SEQ ID NO 26
; LENGTH: 188
; Type: Date of the control of the 
Sequence 35, Application US/07145002B
Patent No. 6482613
GENERAL INFORMATION:
APPLICANT: Goeddel, David V.
APPLICANT: Pestka, Sidney
TITLE OF INVENTION: MICROBIAL PRODUCTION OF MATURE HUMAN
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US-07-145-002B-35
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